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(54) PERCUTANEOUS DELIVERY SYSTEM

TRANSDERMALES VERABREICHUNGSSYSTEM

DISPOSITIF D'ADMINISTRATION PAR VOIE CUTANEE

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Description**FIELD OF THE INVENTION**

5 [0001] The present invention is concerned with a system suitable for the percutaneous delivery, particularly transdermal delivery of active agent. The invention also relates to a method of percutaneous delivery of actives and to therapeutic or prophylactic methods of treatment of a subject by percutaneous delivery of an active agent.

BACKGROUND TO THE INVENTION

10 [0002] The term "active agent" as used herein is intended to denote substances that have a physiological effect, for example, a drug. The term "homogenous" as used herein is intended to mean uniform throughout. The term "film forming" as used herein is intended to mean a substance capable of forming a thin layer on the surface to which it is applied and when exposed to ambient conditions. The term "liquid" as used herein is intended to mean a substance which is flowable. The term "percutaneous" as used herein is intended to mean any route of administering an active agent onto, into or through the skin of a subject so as to achieve one or more of a topical, local or systemic physiological effect.

15 [0003] The use of the skin as a route for delivery of drugs is of relatively recent origin. One form of delivery system is that based on the use of an adhesive transdermal patch. These transdermal patches provide an alternative non-invasive parenteral route for the delivery of drugs which may or may not be suitable for oral administration. An example of an early form of a transdermal patch is described in US patent 3,598,122 where the patch is in the form of a bandage.

20 [0004] Conventional routes of drug administration suffer several disadvantages when compared to the percutaneous route of drug administration. The percutaneous route of delivery may allow for the controlled release of an active agent into the systemic circulation. Many drugs are poorly absorbed by traditional routes of delivery and it has been found that the percutaneous route provides an effective method of achieving improved bioavailability for those active agents.

25 [0005] Examples of the uses of transdermal patches include treatment of nicotine addiction using nicotine containing patches, hormone replacement therapy, treatment of travel sickness using hyoscine, angina using glyceryl trinitrate, treatment of rheumatism using flurbiprofen or ibuprofen, and intractable pain relief using fentanyl. Other examples of transdermal patches are clonidine patches for vasoconstrictor therapy and treatment of migraine (see, for example, US patent 4,201,211), oestradiol patches for treatment of osteoporosis, oestradiol/norethisterone patches, and oestrogen/progesterone patches. The world therapeutic patch market is expected to increase significantly over the next few years.

30 [0006] Existing transdermal patches usually comprise a layer including the active and an adhesive layer and rely on the adhesive layer for attachment of the patch to the skin of a subject. This delivery system involves incorporation of the medicament into a carrier such as a polymeric matrix and/or pressure-sensitive adhesive formulation. The adhesive must adhere to the skin and permit migration of the medicament from the carrier through the skin into the bloodstream of the subject. The medicament may be included in the polymeric matrix or the adhesive layer or both.

35 [0007] An example of an adhesive transdermal delivery system is described in Australian patent 670033. This patent describes a dermal composition comprising a blend of a polyacrylate and a second polymer selected from polysiloxane or a hydrocarbon polymer, wherein the polyacrylate and the second polymer are mutually insoluble or immiscible polymers and a drug wherein the composition is a pressure-sensitive adhesive.

40 [0008] EP 0 219 959 discloses a polymeric hydrogel formulation comprising (1) one or more hydrophilic polymers having an olefinic bond, (2) an α, β-unsaturated carbonyl modified or unmodified amino acid polymer, (3) a crosslinking agent, (4) a lower alkyl (C₁-C₄) alcohol and optionally (5) one or more hydrophobic polymers, and/or (6) a chain regulator. The formulations disclosed are envisaged for use in ophthalmic applications, specifically contact lenses, and in biomedical devices and require UV light induced polymerisation and crosslinking steps in their preparation.

45 [0009] WO 9324105 relates to a topical antiperspirant composition consisting essentially of a non-toxic water insoluble occlusive film-forming antiperspirant polymer. The use of a permeation enhancer in such a composition is disclosed.

50 [0010] Adhesive based transdermal systems suffer a number of disadvantages. A major disadvantage is that the adhesive is responsible for an adverse skin reaction in about 30% of individuals. Current skin patches are occlusive and prevent the skin from transpiring. Moreover the skin area to which the adhesive patch may be applied is restricted to a non-hairy area of the skin that is substantially free of wrinkles, creases and folds. Furthermore, the wearer of an adhesive patch is aware of its presence because of its inability to stretch with the skin on body movement.

55 [0011] In related art there exist topical creams for delivery of active agents for treatment of certain skin diseases. One such disclosure is that of US 4,935,241 in the name of SHIONOGI & CO LTD. This patent describes a pharmaceutical formulation for localised treatment of tinea pedis which comprises a topical cream including an active agent and an ethyl acrylate-methyl methacrylate copolymer.

[0012] An objective of the present invention is to provide a system for the percutaneous delivery of one or more active agents which system avoids, or mitigates at least in part, one or more of the disadvantages attending prior art adhesive transdermal patches. In particular, the compositions developed should be non-occlusive, rate variable and effective in delivering an active agent to have a systemic, topical or local effect upon a subject.

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SUMMARY OF THE INVENTION

[0013] Accordingly, the present invention provides, in one aspect, a substantially homogenous liquid composition for percutaneous delivery of one or more physiologically active agents, the composition comprising at least one physiologically active agent, a volatile solvent, a hydrophilic polymer and a hydrophobic polymer:

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the hydrophilic polymer being selected from the group consisting of hydroxypropylmethyl cellulose, hydroxypropyl cellulose, polyvinyl pyrrolidone, carbomer, PVM/MA decadiene cross polymer and hydroxypropylguar and copolymers thereof, said hydrophilic polymer preferably being present in an amount of from 0.001 to 50% w/w of the total liquid composition and

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the hydrophobic polymer being selected from the group consisting of octylacrylamide acrylate copolymer, aminoalkyl methacrylate copolymer, ammonio methacrylate copolymer, PVPNA copolymer, PVA (polyvinyl acetate), PVM/MA butylester copolymer, shellac and alkyl acrylates and copolymers thereof, said hydrophobic polymer preferably being present in an amount of from 0.001 to 50% w/w of the total liquid composition;

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the combination of hydrophilic and hydrophobic polymers being selected to enable modulation of the rate of delivery of said physiologically active ingredient;

with the proviso that when the hydrophilic polymer is hydroxypropyl cellulose, the hydrophobic polymer is not an ethylacrylate / methyl methacrylate copolymer.

25

[0014] An advantage of the present invention is that the composition of the invention can be dispensed onto, and rubbed into the skin of a subject to form a thin film on the skin surface, this film providing for the percutaneous delivery of the one or more actives contained in the composition. The composition may be applied to the selected skin surface and rubbed onto the skin until a suitable thickness of film is formed. Unlike conventional transdermal patches, the transdermal system of the present invention does not require the use of an adhesive layer. Moreover, it is robust (resistant to accidental removal), waterproof and has good substantivity on the skin. It has additionally been found that the formulations according to the invention can be varied by altering the nature of the modulating polymer combination to alter the rate of release of the active agent into the skin of the patient. In particular it is found that the use of a modulating polymer combination enables the formation of a "reservoir" of active agent on the skin of the patient which can be absorbed by the skin at a varying rate depending on the other components of the formulation.

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[0015] Although it is preferred that the skin surface be non-hairy, the presence of hair does not create as significant a problem as is the case with adhesive patches. Similarly the presence of wrinkles, creases and folds in the skin are not an impediment to the application of the composition of the invention to a particular area of the body, although it is preferable to avoid areas that have significant creasing or folds. Moreover the film that is formed is unobtrusive to the subject in that the subject is not significantly aware of its presence on the skin.

35

[0016] As a hydrophobic polymer and a hydrophilic polymer are used, the composition may be such that when applied to the skin, the volatile solvent may evaporate leaving a two-phase film. The formed film may include a continuous phase and a dispersed phase. The hydrophilic polymer may form the continuous phase and the hydrophobic polymer may form the dispersed phase in the formed film, or *vice versa*.

40

[0017] Alternatively, the hydrophilic polymer may be soluble in the hydrophobic polymer, or *vice versa* so that when the volatile solvent evaporates upon application of the composition to the patient's skin, the remaining film is a single phase.

45

[0018] Where the composition of the invention is used to form a two-phase film, the active agent may be contained in the continuous phase of the film or in the dispersed phase, or in both phases. It is thought that the inclusion of the active agent in the continuous phase of a formed film has the effect of increasing the release rate of the active whereas including the active in the dispersed phase slows down its rate of release.

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[0019] In a preferred aspect, the present invention provides a substantially homogenous liquid composition capable of percutaneous delivery of one or more active agents, the composition including a hydrophilic polymer as defined above and an alkyl olefinic acid amide/olefinic acid or ester copolymer, at least one active agent and a volatile solvent for said hydrophilic polymer and said copolymer and optionally for the said at least one active.

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[0020] In another aspect of the invention, there is provided a substantially homogenous liquid composition, as defined above, and a thickening agent, said thickening agent excluding ethyl cellulose. Preferably said thickening agent is soluble in both water and alcohol. More preferably, the thickening agent is a polymer, preferably a hydrophilic polymer.

[0021] A still further aspect of the invention provides a substantially homogenous liquid composition capable of per-

cutaneous delivery of one or more physiologically active agents, the composition including a volatile solvent, at least one physiologically active agent and a modulating polymer combination of hydrophilic and hydrophobic polymers, wherein the rate of delivery of said physiologically active agent is adjustable by varying the ratio of one of the polymers in said modulating polymer combination with respect to the active agent. A preferred ratio of modulating polymer : active is 1-10,000 : 10,000-1. The ratio will vary according to the potency of the active agent, i.e. how much active agent on a mass basis is required to achieve the physiologically effect desired. For example, for clotrimazole, the ratio of modulating polymer : active agent will be in the order of 1-10 : 10-1.

[0022] A still further aspect of the invention provides a substantially homogenous liquid composition capable of percutaneous delivery of one or more physiologically active agents, the composition including a volatile solvent, at least one physiologically active agent and at least two polymers, one of which is a hydrophobic polymer and one of which is a hydrophilic polymer, wherein the rate of delivery of said physiologically active agent is adjustable by varying the ratio of said hydrophobic polymer with respect to the hydrophilic polymer. A preferred ratio of hydrophobic polymer : hydrophilic polymer is 1-100 : 100-1. A more preferred ratio of hydrophobic polymer : hydrophilic polymer is 1-10 : 10-1.

[0023] The volatile solvent used in the compositions of the invention may be one or more pharmaceutically or veterinary acceptable solvents. The solvent may be present in an amount of at least 50%w/w.

[0024] The compositions of the invention may include one or more skin absorption/penetration enhancers which enhance the absorption and/or penetration of the active agent. The absorption/penetration enhancers may be present in an amount of about 0.1 to 40%w/w of the composition. The absorption/penetration enhancer may be any suitable enhancer known in the art. The enhancer may be a proton accepting solvent. The rate of penetration of the active agent may also be varied by adjusting the rate of release of the penetration enhancer from the polymer.

[0025] The composition of the invention may be in the form of a solution or a dispersion. The composition may also be in the form of a gel.

[0026] Where the composition is in the form of a dispersion, the disperse phase may be in the form of microparticles, microcapsules, microspheres, microsponges or liposomes which may contain and/or be coated with the active agent. Where the dispersed phase is in the form of microparticles, microcapsules, microspheres or liposomes, the continuous phase may include a hydrophobic polymer or a hydrophilic polymer.

[0027] The active agent may be dispersed or dissolved in the composition of the invention and may be present in the composition in a physiologically effective amount. The concentration of active agent used in the composition of the invention may be approximately equivalent to that normally utilised for that particular agent in conventional formulations, particularly that used in conventional transdermal patch delivery systems. The amount of drug to be incorporated in the composition varies depending on the particular drug, the desired therapeutic effect, and the time span for which the device is to provide therapy. For most drugs, the passage of the drugs through the skin will be the rate-limiting step in delivery. Thus, the amount of drug and the rate of release is typically selected so as to provide transdermal delivery characterised by a zero order time dependency for a prolonged period of time. The minimum amount of drug in the system is selected based on the amount of drug which passes through the skin in the time span for which the device is to provide therapy.

[0028] Normally, the amount of drug in the system can vary from about 0.01%w/w to about 50%w/w.

[0029] The compositions may include other components such as stabilisers, plasticisers and waterproofing agents.

[0030] The compositions of the invention may be used in a method for the percutaneous delivery of an active agent, the method including applying a percutaneous composition in accordance with the invention to the skin of the subject. The composition according to the invention may have an anti fungal, anti bacterial or anti viral activity. The subject may be human or an animal.

[0031] Further applications of the invention include methods for the prophylactic or therapeutic treatment of a subject including percutaneously delivering an effective amount of an active agent by application of a composition in accordance with the present invention to the skin of the subject. The subject may be human or animal.

PREFERRED EMBODIMENT OF THE INVENTION

[0032] Examples of suitable volatile solvents include skin safe solvents such as ethanol, isopropanol or acetone.

[0033] Preferably the enhancer is a safe, skin-tolerant ester. Particularly preferred are compounds such as octyl dimethyl para amino benzoate and octyl methoxycinnamate, isoamyl para amino benzoate, octyl salicylate, glyceryl para amino benzoate, triethanolamine salicylate and octocrylene.

[0034] The hydrophilic polymer or the thickening agent are selected from the group consisting of hydroxypropylmethyl cellulose, hydroxypropyl cellulose, polyvinyl pyrrolidone, carborner, PVM/MA decadiene cross polymer and hydroxypropylguar and copolymers thereof.

[0035] The hydrophobic polymer is selected from the group consisting of octylacrylamide acrylate copolymer, aminoalkyl methacrylate copolymer, ammonio methacrylate copolymer, PVPNA copolymer, PVA, PVM/MA butylester copolymer, shellac and alkyl acrylates and copolymers thereof.

- [0036] The overall polymer content of the composition of the invention may be up to 50% w/w.
- [0037] The hydrophilic polymer may be present in an amount of up to about 50% w/w in the composition of the invention.
- [0038] The hydrophilic polymer, or thickening agent may be preferably present in an amount of about 0.5 to 30% w/w of the composition of the invention. More preferably, the hydrophilic polymer is present in an amount of 0.05 to 10% w/w of the composition, most preferably 1.0 to 5.0% w/w of the composition.
- [0039] The hydrophobic polymer may be present in an amount up to about 50% w/w. The hydrophobic polymer may be present in an amount of about 0.001 to 30% of the composition of the invention. Preferably, the hydrophobic polymer is present in an amount of 1.0 to 10% of the composition, more preferably 1.5 to 6.0%.
- [0040] The active agent may be any suitable compound. The active agent may be a pharmaceutical or veterinary agent. The active agent may be a drug that is normally delivered by oral, parenteral, percutaneous or rectal route. The active agent may be a prodrug.
- [0041] Examples of active drugs that can be administered by the novel transdermal drug delivery system of this invention include, but are not limited to:
- 15 Cardioactive medications, for example, organic nitrates such as nitroglycerine, isosorbide dinitrate, and isosorbide mononitrate; quinidine sulfate; procainamide; thiazides such as bendroflumethiazide, chlorothiazide, and hydrochlorothiazide; nifedipine; nicardipine; adrenergic blocking agents, such as timolol and propranolol; verapamil; diltiazem; captopril; clonidine and prazosin.
- 20 Androgenic steroids, such as testosterone, methyltestosterone and fluoxymesterone.
- Estrogens, such as conjugated estrogens, esterified estrogens, estropipate, 17beta estradiol, 17beta-estradiol valerate, equilin, mestranol, estrone, estriol, 17beta-ethinyl estradiol, and diethylstilboestrol. Progestational agents, such as progesterone, 19-norprogesterone, norethindrone, norethindrone acetate, melengestrol, chlormadinone, ethisterone, medroxyprogesterone acetate, hydroxyprogesterone caproate, ethynodiol diacetate,
- 25 norethynodrel, 17alpha hydroxyprogesterone, dydrogesterone, dimethisterone, ethynodiol, norgestrel, demegestone, promegestone, and megestrol acetate.
- Drugs having an action on the central nervous system, for example sedatives, hypnotics, antianxiety agents, analgesics and anaesthetics, such as chloral, buprenorphine, naloxone, haloperidol, fluphenazine, pentobarbital, phenobarbital, secobarbital, codeine, lidocaine, tetracaine, dyclonine, dibucaine, methocaine, cocaine, procaine, mepivacaine, bupivacaine, etidocaine, prilocaine, benzocaine, fentanyl, and nicotine.
- 30 Nutritional agents, such as vitamins, essential amino acids and essential fats.
- Anti-inflammatory agents, such as hydrocortisone, cortisone, dexamethasone, flucinolone, triamcinolone, medrysone, prednisolone, flurandrenolide, prednisone, halcinonide, methylprednisolone, flurandrenolide, prednisone, halcinonide, methylprednisolone, fludrocortisone, corticosterone, paramethasone, betamethasone, ibuprofen, naproxen, fenoprofen, fenbufen, flurbiprofen, indoprofen, ketoprofen, suprofen, Indomethacin, piroxicam, aspirin, salicylic acid, diflunisal, methyl salicylate, phenylbutazone, sulindac, mefenamic acid, meclofenamate sodium, tolmetin, and the like.
- 35 Antihistamines, such as diphenhydramine, dimenhydrinate, perphenazine, triprolidine, pyrilamine, chlorcyclizine, promethazine, carbinoxamine, triplettamine, brompheniramine, hydroxyzine, cyclizine, meclizine, clorpheniramine, terfenadine, and chlorpheniramine.
- 40 Respiratory agents, such as theophylline and beta2-adrenergic agonists such as albuterol, terbutaline, metaproterenol, ritodrine, carbuterol, fenoterol, quinterenol, rimiterol, solmefamol, soterenol, and tetroquinol.
- Sympathomimetics, such as dopamine, norepinephrine, phenylpropanolamine, phenylephrine, pseudoephedrine, amphetamine, propylhexedrine and epinephrine. Miotics, such as pilocarpine, and the like. Cholinergic agonists, such as choline, acetylcholine, methacholine, carbachol, bethanechol, pilocarpine, muscarine, and arecoline.
- 45 Antimuscarinic or muscarinic cholinergic blocking agents such as atropine, scopolamine, homatropine, methscopolamine, homatropine methylbromide, methantheline, cyclopentolate, tropicamide, propantheline, anisotropine, dicyclomine, and eucatropine. Mydriatics, such as atropine, cyclopentolate, homatropine, scopolamine, tropicamide, eucatropine and hydroxyamphetamine.
- 50 Psychic energizers such as 3-(2-aminoethyl)indole, 3-(2-aminobutyl)indole, and the like.
- Anti-Infectives, such as antibiotics, including penicillin, tetracycline, chloramphenicol, sulfacetamide, sulfamethazine, sulfadiazine, sulfamerazine, sulfamethizole and sulfisoxazole; antivirals, including idoxuridine; antibacterials, such as erythromycin and clarithromycin; and other anti-infectives including nitrofurazone and the like.
- Dermatological agents, such as vitamins A and E.
- 55 Humoral agents, such as the prostaglandins, natural and synthetic, for example PGE1, PGF2alpha, and PGF2alpha, and the PGE1 analog misoprostol.
- Antispasmodics, such as atropine, methantheline, papaverine, cinnamedrine, and methscopolamine.
- Antidepressant drugs, such as isocarboxazid, phenelzine, tranylcypromine, imipramine, amitriptyline, trimipramine,

doxepin, desipramine, nortriptyline, protriptyline, amoxapine, maprotiline, and trazodone.
 Anti-diabetics, such as insulin, and anticancer drugs such as tamoxifen and methotrexate.
 Anorectic drugs, such as dextroamphetamine, methamphetamine, phenylpropanolamine, fenfluramine, diethylpropion, mazindol, and phentermine.

5 Anti-allergics, such as antazoline, methapyrilene, chlorpheniramine, pyrilamine and pheniramine.
 Tranquilizers, such as reserpine, chlorpromazine, and antianxiety benzodiazepines such as alprazolam, chlordiazepoxide, clorazeptate, halazepam, oxazepam, prazepam, clonazepam, flurazepam, triazolam, lorazepam and diazepam.

10 Antipsychotics, such as thiopropazate, chlorpromazine, trifluopromazine, mesoridazine, piperacetazine, thioridazine, acetophenazine, fluphenazine, perphenazine, trifluoperazine, chlorprathixene, thiothixene, haloperidol, bromperidol, loxapine, and molindone.
 Decongestants, such as phenylephrine, ephedrine, naphazoline.
 Antipyretics, such as aspirin, salicylamide, and the like.
 Antimigraine agents, such as dihydroergotamine and pizotyline.

15 Drugs for treating nausea and vomiting, such as chlorpromazine, perphenazine, prochlorperazine, promethazine, triethylperazine, trifluopromazine, and trimeprazine.
 Anti-malarials, such as the 4-aminoquinolines, alpha-aminoquinolines, chloroquine, and pyrimethamine.
 Anti-ulcerative agents, such as misoprostol, omeprazole, and enprostil.

20 Peptides and proteins, such as drugs for Parkinson's disease, spasticity, and acute muscle spasms, such as levodopa, carbidopa, amantadine, apomorphine, bromocriptine, selegiline (deprenyl), trihexyphenidyl hydrochloride, benztropine mesylate, procyclidine hydrochloride, baclofen, diazepam, dantrolene, insulin, erythropoietin and growth hormone.
 Anti-estrogen or hormone agents, such as tamoxifen or human chorionic gonadotropin.
 Nucleotides and nucleic acids (eg. DNA).

- 25 [0042] The active agents can be present in the composition in different forms, depending on which form yields the optimum delivery characteristics. Thus, in the case of drugs, the drug can be in its free base or acid form, or in the form of salts, esters, or any other pharmacologically acceptable derivatives, or as components of molecular complexes.
- 30 [0043] The utility of the invention is described as follows using various examples and graphs. The examples are by no means extensive and do not set boundaries for the invention in any way. The purpose of the examples is to provide evidence of the function of the invention and advantages thereof.
- [0044] In the examples provided, the effectiveness of the composition according to the invention as a diffusion controlling film is shown. It can be demonstrated that the system can be used with transdermal penetration enhancers to modify the transdermal flux rate of active molecules. It can also be used with or without penetration enhancers to effectively retain active substances on the top layers of skin or to provide a sustained rate of release of active into the skin.
- [0045] Some examples also highlight the ability of the system to provide wash resistance.

BRIEF DESCRIPTION OF THE FIGURES

- 40 [0046] Figure 1 is a plot of the percent of applied dose of Ibuprofen transferred across shed snake skin *in vitro* from different gel formulations according to the invention. The error bars represent the SEM (Standard Error of the Mean).
 [0047] Figure 2 is a plot of the percent of the applied dose transferred across shed snake skin *in vitro* from Flurbiprofen gels. The error bars represent the SEM.
- 45 [0048] P = 0.002 (paired t-test relative to control).
 [0049] Figure 3 is a plot of the percent of applied dose of Ketoprofen transferred across shed snake skin *in vitro* from different gel formulations according to the invention. The error bars represent the SEM.
 [0050] Figure 4 is a graph of the percent of applied dose of Canesten™ and a formulation according to the invention retained on the skin after a given time and under given conditions.
- 50 [0051] Figure 5 is a plot of the percent of applied dose transferred across skin *in vitro* from Ketoprofen gels according to the invention in which the nature of the hydrophobic polymer has been altered. The error bars represent the SEM.
 [0052] Figure 6 is a plot of the percent of applied dose transferred across skin *in vitro* from Diclofenac gels according to the invention.

55 EXAMPLE A

- [0053] A composition in accordance with the invention was prepared by combining the following components in a stirred vessel at ambient temperature:

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Component	Amount (w/w)
Ketoprofen	2.5%
Klucel (hydroxypropyl cellulose)	3.0%
Acrylate/octylacrylamide copolymer	3.8%
Alcohol 100	90.7%

5 [0054] The composition formed was in the form of a clear solution. When applied to the skin and spread out on the
10 skin surface formed a substantially clear thin film.

EXAMPLE B

15 [0055]

Component	Amount (w/w)
Ketoprofen	2.5%
Klucel (hydroxypropyl cellulose)	2.5%
Acrylate/octylacrylamide copolymer	3.0%
* Benzyl Benzoate	3.0%
Alcohol to	100%

* enhancer

25 **EXAMPLE C**

[0056]

Component	Amount (w/w)
Ibuprofen	2.5%
Klucel G	3.0%
Ethanol	to 100%

35 **IN VITRO DIFFUSION MEASUREMENTS**

Shed Snake Skin.

40 [0057] The Children's Python shed snake skin was obtained during natural shedding and the dorsal skin was used. Shed snake skin has shown to be a suitable model membrane for human skin by Itoh, et al., Use of Shed Snake Skin as a Model Membrane for In Vitro Percutaneous Penetration Studies: Comparison with Human Skin Pharm. Res., 7 (10), 1042-1047, 1990; and Rigg, et al; Shed Snake Skin and Hairless Mouse Skin as Model Membranes for Human Skin During Permeation Studies, J. Invest. Dermatol., 94; 235-240, 1990.

45 **METHOD OF CONDUCTING IN-VITRO SKIN DIFFUSION EXPERIMENTS IN HORIZONTAL DIFFUSION CELLS**

[0058] A modified stainless steel flow-through diffusion cell assembly based on that first shown by Cooper in J.Pharm. Sci. 73, 1984, was used to perform the experiments on diffusion of the drugs from various donor compositions through snake skin.

50 [0059] Topical formulations are weighed out onto the skin substrate which has an area of 0.79cm². Active substance penetrates through the skin and into the receptor solution in the bottom section of the cell. inlet and outlet tubes connected to the receptor chamber maintain skin conditions.

[0060] The temperature of the skin was maintained at 32°C

55 [0061] The receptor solution consisted of 50% propylene glycol in water, made isotonic with 0.9% sodium chloride and preserved with 0.1% sodium azide.

[0062] The concentration of applied drug in each diffusion cell sample was measured using high pressure liquid chromatography (HPLC) and absorbance detection. The results reported for each experiment are average values of

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the replicate diffusion cells. The assay conditions used for each different drug are given in each example.

EXAMPLE 1

- 5 [0063] The in vitro diffusion cell method described above was used to demonstrate that ibuprofen penetrates through skin using this system. The formulations tested are described in the table below.

Material	Gel 1 % w/w	Gel 2 % w/w	Gel 3 % w/w	Control % w/w
Ibuprofen	5.0	5.0	5.0	5.0
Octyl Salicylate	5.0	3.0	5.0	3.0
Hydroxypropyl				
Cellulose	2.2	2.2	2.2	2.2
Acrylates/octylacrylamide copolymer	0.001	0.001	0.001	
Water	-	20.0	15.0	23.8
Ethanol	to 100.0	to 100.0	to 100.0	to 100.0

20 [0064] Samples were assayed as per the method described earlier.

[0065] The detection wavelength was 210nm and the mobile phase consisted of 60% acetonitrile, 0.1% H_3PO_4 ; pH = 3 adjusted with NaOH.

[0066] Figure 1 shows the plot of percent dose transferred versus time for the respective formulations. Error bars represent the standard error of the mean.

EXAMPLE 2

[0067] The same in-vitro diffusion cell method described was also used to demonstrate that flurbiprofen (another NSAID-Non Steroidal Anti Inflammatory Drug) penetrates skin from this system.

[0068] The following formulations were tested:

Material	Control % w/w	F65/57/02 % w/w
Flurbiprofen	5.0	5.0
Acrylates/octylacrylamide copolymer	0.001	0.001
Hydroxypropyl		
Cellulose	2.2	2.2
Octyl Salicylate	-	5.0
Deionised Water	15.0	15.0
Ethanol 95%	77.7	72.7

[0069] Samples were assayed according to the general procedure outlined earlier.

[0070] The detection wavelength was 247nm and the mobile phase consisted of 60% acetonitrile, 0.1 % H_3PO_4 at pH 3 adjusted with NaOH.

[0071] Figure 2 shows the plot of % dose transferred versus time for the formulations. Error bars represent the standard error of the mean.

EXAMPLE 3

[0072] In vitro penetration studies were used to demonstrate that ketoprofen penetrates skin and that the rate of penetration could be modified by inclusion of higher levels of Acrylates/octylacrylamide copolymer.

[0073] The formulations tested were as follows:

Material	71/05/01 % w/w	71/05/02 % w/w	71/05/03 % w/w	71/05/04 % w/w	71/05/05 % w/w
Ketoprofen	2.5	5.0	2.5	2.5	2.5

(continued)

Material	71/05/01 % w/w	71/05/02 % w/w	71/05/03 % w/w	71/05/04 % w/w	71/05/05 % w/w
Octyl Salicylate	2.5	5.0	2.5	2.5	-
Acrylates/octylacrylamide copolymer	0.05	0.05	2.5	10.0	0.05
Klucel™	2.2	2.2	2.2	2.2	2.2
Ethanol 95%	to 100.0				

- [0074] Figure 3 shows the plot of % dose transferred versus time for each formulation. This shows that by adjusting the ratio of the modulating polymer:active and/or hydrophobic polymer:hydrophilic polymer, the rate of the release of Ketoprofen into the skin of the subject can be varied. In particular, the graph demonstrates that the penetration enhancement can be controlled by varying the level of Acrylates/octylacrylamide copolymer in the gel.
- [0075] Samples were assayed according to the general procedure outlined earlier. The detection wavelength was 255nm and the mobile phase consisted of 55% acetonitrile, 0.1% H₃PO₄ at pH 3 adjusted with NaOH.

EXAMPLE 4

- [0076] In order to demonstrate the ability of the composition according to the invention to produce water resistant films capable of increasing the skin substantivity of actives the following testing was conducted.
- [0077] An in vivo experiment was conducted on a 1% clotrimazole gel according to the invention versus commercial clotrimazole cream (1% clotrimazole) to test for substantivity and wash resistance.
- [0078] The gel formulation according to the invention was as follows:

2.5% w/w	Klucel™ (Hydroxypropylcellulose)
3.2% w/w	Acrylates/octylacrylamide copolymer
1.0% w/w	Clotrimazole
to 100% w/w	Ethanol

- [0079] Each product was applied to the forearm of the subject and allowed to dry thoroughly.
- [0080] At 6 and 24 hours after application the active remaining on the skin was extracted using warm ethanol.
- [0081] A further condition used was a thirty second immersion in a soap solution at the 10 hour time point.
- [0082] The results of the trial are depicted in Figure 4.
- [0083] The results clearly demonstrate that significantly more clotrimazole remains on the skin after application of the gel compared with the commercial clotrimazole cream.
- [0084] In fact greater than 50% of clotrimazole originally applied is still present after 24 hours compared with approximately 5% for the commercial clotrimazole cream.
- [0085] Further, the results demonstrate the wash resistance of the gel.
- [0086] The soaking of the film removed only a small portion of clotrimazole from the gel formulation whereas after soaking the commercial clotrimazole cream, only about 1% of the original dose of clotrimazole remained.

EXAMPLE 5

- [0087] To demonstrate the activity of clotrimazole in the gel formulation according to the invention after application the following experiment was conducted.
- [0088] A series of 1% clotrimazole gels prepared according to the invention and a commercial 1% clotrimazole cream were subjected to a zone of inhibition test against Candida albicans.
- [0089] The gels and cream were applied to round glass cover slips of 5cm² each. The application rate for all products was 5mg/cm².
- [0090] After drying, the coated side of the slides were placed on MEA plates which had been previously seeded with a culture of C. albicans. The plates were incubated at 37°C for 72 hours. The zone of inhibition was measured around the test slips at the end of the incubation period. Furthermore the slips were removed and an assessment of the growth of the test organism was made in the contact zone with the slips. All tests were performed in duplicate.
- [0091] The formulations tested were as follows:

Material	F65/22/02 % w/w	F65/22/01 % w/w	F65/53/01 % w/w	F65/53/02 % w/w
Clotrimazole	-	1.00	1.00	-
Klucel™	2.50	2.50	2.50	2.50
Acrylates/octylacrylamide copolymer	3.20	3.20	-	-
Propylene				
Glycol			5.00	5.00
Ethanol	to 100.0	to 100.0	to 100.0	to 100.0

[0092] The results of the testing are shown in the following table.

Sample Description	Inhibition in Contact Zone	Zone mm
A commercial 1% clotrimazole Cream B.6C04 Exp. 3/98	Almost Complete	1, 1
Placebo Clotrimazole Gel Form No. F65/22/02 B/N E65/22/02	No Inhibition	0, 0
Clotrimazole 1% Gel Form No. F65/22/01 B/N E65/22/01	Almost Complete	4, 4
Clotrimazole 1% Gel Form No. 65/53/01	Complete	8, 9
Placebo Gel F65/53/02	Partial	0, 0

[0093] The results clearly demonstrate that the clotrimazole is biologically active within the film according to the invention and in fact is more active than the commercial clotrimazole cream.

[0094] Further, the activity of clotrimazole could be increased by addition of a plasticiser ie., propylene glycol.

EXAMPLE 6

[0095] As a demonstration of the ability to use a variety of thickeners in this invention the following formulations were prepared.

Material	F71/37/06 %w/w	F71/37/07 %w/w	F71/37/10 %w/w	F71/37/11 %w/w	F71/37/13 %w/w	F71/57/01 %w/w
Carbopol™ Ultrez 10	0.3	0.5	-	-	-	-
Triethanolamine	0.3	-	0.4	-	-	-
PVP/VA 335 (50%)	6.0	-	6.0	-	6.0	-
Deionised Water	30.0	20.0	30.0	-	30.0	20.0
Tributylamine	-	0.7	-	-	-	-
Eudragit™ E	-	3.0	-	-	-	3.0
Stabileze™ 06	-	-	0.7	2.0	-	-
Eudragit™ RL PO	-	-	-	3.0	-	-
Ethomeen™ C25	-	-	-	4.0	-	-
Hydroxypropyl-methylcellulose	-	-	--		2.50	-

(continued)

	F71/37/06	F71/37/07	F71/37/10	F71/37/11	F71/37/13	F71/57/01
5	Jaguar™ HP-120	-	-	-	-	2.0
	Citric Acid	-	-	-	-	0.055
	Ethanol 95%	to 100.0				
Carbopol™ Ultrez10 = Carbomer PVPNA 335 = 50% solution of PVPNA Eudragit™ E = Aminoalkyl methacrylate copolymer Stabileze™ 06 = PVM/MA decadiene cross polymer Eudragit™ RLPO = Ammonio Methacrylate Copolymer Ethomeen™ C25 = PEG 15 Cocamine Jaguar™ HP-120 = Hydroxypropyl guar						

[0096] The respective viscosities of the gels made according to the invention was measured at 25°C with a Brookfield RVT viscometer.

[0097] They were as follows:

- Viscosity (F71/37/06, spindle 3, 10 rpm) = 2,500 cps.
- Viscosity (F71/37/07, spindle 5, 2.5 rpm) = 112,000 cps.
- Viscosity (F71/37/10, spindle 4, 5 rpm) = 76,000 cps.
- Viscosity (F71/37/11, spindle 4, 2.5 rpm) = 40,800 cps.
- Viscosity (F71/37/13, spindle 6, 5 rpm) = 102,000 cps.
- Viscosity (F71/57/01, Spindle 4, 10 rpm) = 10,000 cps.

[0098] These viscosity measurements demonstrate that various thickeners can be used to produce suitable gels with a variety of hydrophobic polymers.

EXAMPLE 7 - COMPARATIVE EXAMPLE

[0099] The gel described by Shionogi, Patent Number 4,935,241 dated June 19, 1990, and entitled Pharmaceutical Preparation for Tinea Pedis has a cosmetically unacceptable base due to:

- Lack of viscosity from ethyl cellulose making it difficult to apply.
- Incompatibility between HPC or HPMC and EA/MMA.

[0100] In order to overcome these shortcomings a gel was prepared using Hydroxypropylcellulose and a compatible polymer, Acrylates/octylacrylamide copolymer.

[0101] This product had the advantage of:

- Complete miscibility between the two polymers in solution (HPC and Acrylates/octylacrylamide copolymer).
- The gel could be prepared at a large range of viscosities ie, from 100 cps to 200,000 cps depending on molecular weight and percentage of HPC used.

[0102] Hence this product had the advantage of both clarity, homogeneity and ease of application.

[0103] To test the utility of the adapted gel formulation to deliver actives into skin an in-vitro skin absorption experiment was conducted comparing the absorption of clotrimazole (an antifungal) from the composition according to the invention, Shionogi base and a commercial clotrimazole cream. All preparations contained 1% clotrimazole.

[0104] The gel formulations used are shown below.

	F65/64/01	Shionogi Base F71/17/02
Material	% w/w	% w/w
Clotrimazole	1.00	1.00

(continued)

	F65/64/01	Shionogi Base F71/17/02
	% w/w	% w/w
5	Klucel™	2.50
	Acrylates/octylacrylamide copolymer	3.20
10	Ethyl Cellulose	-
	Eudragit™ NE40D	1.00
	Ethanol 95%	10.0
	Eudragit™ NE 40D = 40% dispersion of ethylacrylate/methyl-methacrylate	
	to 100.0	
	to 100.0	

15 [0105] These formulations were compared for skin penetration, and epidermal and dermal retention using the following procedure.

CLOTRIMAZOLE TEST METHOD AND TABLE OF RESULTS

20 **Method:**

Equipment & Materials:

[0106]

- 25 • in-vitro Franz diffusion cell with full thickness human skin (surface area 1.23cm², receptor volume 3.5ml)
 • HPLC equipment: Shimadzu automated HPLC system with UV detection
 • bovine serum albumin (BSA) dissolved in phosphate buffered saline (pH

30 7.4) as receptor phase to mimic physiological conditions.

Experimental Protocol:

[0107]

- 35 • finite dosing (50mg of each formulation)
 • receptor phase: 4% BSA in PBS at pH 7.4
 • sampling time: 0, 6, 10 and 24 hours (amount in receptor phase)
 • epidermis separated from the dermis following 24 hour exposure to formulation
 40 • non occlusive study
 • each time period and formulation conducted in triplicate

Application Procedure

45 [0108]

- 50mg of each formulation was applied to the exposed skin surface at time 0 min
- Procedure was the same for all products

50 **HPLC Assay**

[0109] Active content determined by HPLC assay using a detection wavelength of 210nm.

[0110] The following table shows cumulated clotrimazole concentration in receptor phase ($\mu\text{g}/\text{cell}$) at 0, 6, 10 and 24 hours and in the epidermis and dermis ($\mu\text{g}/\text{cm}^2$) following application of clotrimazole gels (F65/64/01 and F71/17/02) and a commercial clotrimazole cream.

Formulation	Receptor				Epidermis at 24 hrs	Dermis at 24 hrs
	0 hrs	6 hrs	10 hrs	24 hrs		
1. The composition according to the invention (F65/64/01)						
1A	N	N	N	N	114.23	1.72
1B	N	N	N	N	64.01	2.37
1C	N	N	N	N	69.89	2.60
Mean ± Standard Deviation					82.71 ± 27.45	2.23 ± 0.46
2. Clotrimazole Gel (Shionogi base) (F71/17/02)						
2A	N	N	N	N	19.10	2.49
2B	N	N	N	N	23.29	2.33
2C	N	N	N	N	28.67	1.99
Mean ± Standard Deviation					23.69 ± 4.79	2.27 ± 0.26
3. Commercial 1% clotrimazole cream						
3A	N	N	N	N	8.66	0.92
3B	N	N	N	N	18.66	1.39
3C	N	N	N	N	13.88	0.86
Mean ± Standard Deviation					13.74 ± 5.0	1.06 ± 0.29
N = Not Detectable						

Statistical Analysis

[0111] Epidermal and dermal retention of clotrimazole following applications of each of the formulations was compared by oneway ANOVA with posthoc follow-up using Tukey-HSD (sig p<.05).

[0112] *Epidermal retention:* Formulation 1 (clotrimazole gel F65/64/01) demonstrated significantly greater epidermal retention of clotrimazole than the other formulations tested.

[0113] *Dermal retention:* Formulations 1 and 2 (clotrimazole gels) demonstrated significantly greater dermal retention of clotrimazole than the commercial clotrimazole cream.

[0114] The following observations were thus made:

1. None of the formulations tested had detectable skin penetration to the receptor phase up to and including at 24 hours following application.
2. The epidermal concentrations of clotrimazole in decreasing order were Formulation 1 (F65/64/01 - a product according to the invention), Formulation 2 (F71/17/02 - Shionogi base) and Formulation 3 (commercial 1% clotrimazole cream). The epidermal retention of formulation 1 was significantly greater than that of the other two formulations tested.
3. The dermal concentrations of formulation 1 and 2 were similar and were significantly higher than that of the commercial clotrimazole cream.

[0115] These results were surprising and clearly demonstrate the superiority of the composition according to the invention system to deliver more clotrimazole into skin over a 24 hour period. Also the composition according to the invention was far more effective than a commercial cream for delivery of clotrimazole.

[0116] This work coupled with results shown in example 4 demonstrate that the compositions according to the invention are not only more substantive to top layers of skin but also deliver more active into skin than the commercial clotrimazole cream.

EXAMPLE 8

[0117] To demonstrate the ability of a range of hydrophobic polymers to modify the penetration of actives through skin the following experimentation was conducted.

- 5 [0118] Six different hydrophobic polymers were prepared in a base composition according to the invention using ketoprofen as the active and octyl salicylate as the penetration enhancer.
[0119] These were tested for in-vitro transdermal penetration using baby snake skin as described previously.
[0120] The following formulations were prepared:

10	Material	F71/24/01 % w/w	F71/24/02 % w/w	F71/24/03 % w/w	F71/24/04 % w/w
	Ketoprofen	2.50	2.50	2.50	2.50
	Octyl Salicylate	2.50	2.50	2.50	-
15	Klucel™	2.20	2.20	2.20	2.20
	PVP/VA (50%)	20.0	-	-	-
	Eudragit™ E	-	10.0	-	-
	Shellac	-	-	10.0	-
20	Acrylates/octylacrylamide copolymer	-	-	-	10.0
	Ethanol 95%	to 100.0	to 100.0	to 100.0	to 100.0

25	Material	F71/24/05 % w/w	F71/24/06 % w/w	F71/24/07 % w/w	F71/24/08 % w/w
	Ketoprofen	2.50	2.50	2.50	2.50
	Octyl	2.50	2.50	2.50	2.50
	Salicylate	-	2.20	2.20	2.20
30	Klucel™ M	12.20	-	-	-
	Klucel™ JFF	-	-	10.00	-
	Amphomer™	-	-	-	-
	Gantrez™	-	-	-	-
	ES 425 (50%)	-	-	-	20.0
35	Ethanol 95%	to 100.0	to 100.0	to 100.0	to 100.0
	Klucel™ = Hydroxypropylcellulose				
	Amphomer™ = Octylacrylamide/acrylates/butylaminoethyl methacrylate copolymer				
	Gantrez™ ES 425 = Butyl ester of PVM/MA copolymer				

40 [0121] The results of penetration from these gels are shown graphically in figure 5 wherein the % dose transferred is plotted versus time.

[0122] These results demonstrate that the penetration of ketoprofen can be controlled through the incorporation of hydrophobic polymers.

EXAMPLE 9

45 [0123] This example demonstrates that the composition according to the invention may also be used as a vehicle for anti-viral compounds. The active in this case was penciclovir. A gel was prepared according to the following formulation.

55		% w/w
	Penciclovir	0.30
	Acrylates/octylacrylamide copolymer	3.0
	N methyl pyrrolidone	30.0
	Klucel™ M	2.20

(continued)

	% w/w
5 Deionised Water	14.50
	Isopropyl alcohol
	50.0

[0124] This product was a clear viscous, colourless, homogenous gel suitable for application to skin to produce a localised anti-viral effect.

10 **EXAMPLE 10**

[0125] To further demonstrate the utility of the composition according to the invention for delivering NSAID's through skin, the in-vitro diffusion cell method described previously was used to assess penetration of diclofenac.

15 [0126] The following formulations were tested.

		Control Solution % w/w	F63/55/01 % w/w
20	Acrylates/octylacrylamide copolymer	-	0.001
	Klucel™	-	2.20
	Octyl Dimethyl PABA	-	1.16
	Diclofenac		
25	Diethylammonium	1.16	1.16
	Water	30.0	-
	Ethanol	to 100.0	to 100.0

[0127] The skin penetration results from the formulations are shown graphically in Figure 6.

30 **EXAMPLE 11 - COMPARATIVE DESCRIPTION OF SHIONOGI PATENT GELS**

[0128] The purpose of this example is to demonstrate that the gels of US Patent Number 4,935,241 dated June 19, 1990, and entitled "Pharmaceutical Preparation for Tinea Pedis" do not meet the criteria of the compositions according to the present invention, i.e. homogeneity during storage.

	Material	F71/46/04 % w/w	F71/46/05 % w/w	F71/46/06 % w/w
35	Ethyl Cellulose	1.00	-	-
40	EA/MMA (40% dispersion)	10.00	10.00	10.00
	Hydroxypropyl-methylcellulose	-	1.00	-
	Hydroxypropylcellulose	-	-	1.00
	Deionised water	22.20	22.20	22.20
45	Isopropyl alcohol	to 100.0	to 100.0	to 100.0

[0129] Appearance of gels after one week of storage at room temperature was as follows.

F71/46/04

50 [0130] Thin clear gel with a fine flocculated precipitate which had settled on bottom.

F71/46/05

[0131] Translucent, thin, lumpy gel with some solid white lumps.

55

F71/46/06

[0132] Clear gel which separated into two clear layers.

5

Claims

1. A substantially homogeneous liquid composition for percutaneous delivery of one or more physiologically active agents, the composition being capable of being applied to a selected skin surface in a manner so as to form *in situ* a film of the composition that adheres to said skin surface, the composition comprising at least one physiologically active agent, a volatile solvent, a hydrophilic polymer and a hydrophobic polymer: the hydrophilic polymer being selected from hydroxypropylmethyl cellulose, hydroxypropyl cellulose, polyvinyl pyrrolidone, carborer, PVM/MA decadiene cross polymer and hydroxypropylguar and copolymers thereof; and
the hydrophobic polymer being selected from octylacrylamide acrylate copolymer, aminoalkyl methacrylate copolymer, ammonio methacrylate copolymer, PVP/VA copolymer, PVA, PVM/MA butylester copolymer, shellac and alkyl acrylates and copolymers thereof;
such that in use the hydrophilic and hydrophobic polymers present in the composition are capable of modulating the rate of delivery of said physiologically active ingredient; with the proviso that when the hydrophilic polymer is hydroxypropyl cellulose, the hydrophobic polymer is not an ethylacrylate/methyl methacrylate copolymer.
2. A liquid composition as claimed in Claim 1 and further comprising a penetration enhancer.
3. A liquid composition as claimed in Claim 1 or 2, wherein the hydrophilic polymer is capable of forming a continuous phase when applied to the skin of a subject and the hydrophobic polymer is dispersed or soluble therein.
4. A liquid composition as claimed in Claim 1 or 2, wherein the hydrophobic polymer is capable of forming a continuous phase when applied to the skin of a subject and the hydrophilic polymer is dispersed or soluble therein.
5. A liquid composition as claimed in Claim 3 or 4, wherein said physiologically active agent is contained in said continuous phase.
6. A liquid composition as claimed in Claim 3 or 4, wherein the composition is in the form of a dispersion and wherein said physiologically active agent is contained in said dispersed phase.
7. A liquid composition as claimed in any preceding claim, wherein said hydrophilic polymer is a hydroxyalkyl cellulose.
8. A liquid composition as claimed in Claim 7, wherein said hydrophilic polymer is hydroxypropyl cellulose.
9. A liquid composition as claimed in any preceding claim, wherein said hydrophobic polymer is octylacrylamide acrylate copolymer.
10. A liquid composition as claimed in any one of Claims 1 to 8, wherein the hydrophobic polymer is an amino alkyl methacrylate copolymer.
11. A liquid composition as claimed in any preceding claim, wherein the rate of delivery of said physiologically active agent is adjustable by varying either the ratio of hydrophilic polymer to active agent or the ratio of hydrophobic polymer to active agent.
12. A liquid composition as claimed in any one of Claims 1 to 10, wherein the rate of delivery of said physiologically active agent is adjustable by varying the ratio of hydrophilic polymer to hydrophobic polymer.
13. A liquid composition as claimed in any preceding Claim and further comprising a thickening agent other than ethyl cellulose.
14. A liquid composition as claimed in Claim 13, wherein said thickening agent is a polymer soluble in both alcohol and water.
15. A liquid composition as claimed in any preceding Claim, wherein the total polymer content of the composition is

up to 50% w/w

Patentansprüche

- 5 1. Eine im wesentlichen homogene flüssige Zusammensetzung zur perkutanen Zuführung eines von mehreren physiologisch wirksamen Wirkstoffen, wobei die Zusammensetzung in der Lage ist, auf einen bestimmten Hautoberflächenbereich aufgetragen zu werden, und zwar auf eine Weise, daß *in situ* eine Schicht der Zusammensetzung gebildet wird, die an der besagten Hautoberfläche haftet, wobei die Zusammensetzung zumindest aus einem physiologisch aktivem Wirkstoff, einem flüchtigen Lösungsmittel, einem hydrophilen Polymer und einem hydrophoben Polymer besteht; dabei wird der hydrophile Polymer von Hydroxypropylmethylzellulose, Hydroxypropylzellulose, Polyvinylpyrrolidon, Carbomer, PVM/MA Decadien-Crosspolymer und Hydroxypropylguar und Copolymeren von diesen Stoffen ausgewählt; und dabei wird der hydrophobe Polymer von Octylacrylamid-Acrylat-Copolymer, Aminoalkyl-Methacrylat-Copolymer, Ammonio-Methacrylat-Copolymer, PVP/VA-Copolymer, PVA, PVM/MA-Butylester-Copolymer, Schellack und Alkyl-Acrylaten und Copolymeren von diesen Stoffen ausgewählt; und zwar so, daß bei der Anwendung die in der Zusammensetzung vorhandenen hydrophilen und hydrophoben Polymere die Zuführungsgeschwindigkeit des besagten physiologisch aktiven Inhaltsstoffes verändern können; mit der Einschränkung, daß wenn es sich bei dem hydrophilen Polymer um Hydroxypropylzellulose handelt, es sich bei dem hydrophoben Polymer nicht um einen Äthylacrylat-/Methylmethacrylat-Copolymer handelt.
- 10 2. Flüssige Zusammensetzung gemäß Patentanspruch 1, die desweiteren ein Eindringungsverstärkungsmittel beinhaltet.
- 15 3. Flüssige Zusammensetzung gemäß Patentanspruch 1 oder 2, wobei der hydrophile Polymer eine ständige Phase bilden kann, wenn er auf die Haut einer Person aufgetragen wird, und der hydrophobe Polymer darin verteilt wird, bzw. darin gelöst ist.
- 20 4. Flüssige Zusammensetzung gemäß Patentanspruch 1 oder 2, wobei der hydrophobe Polymer eine ständige Phase bilden kann, wenn er auf die Haut einer Person aufgetragen wird, und der hydrophile Polymer darin verteilt wird, bzw. darin gelöst ist.
- 25 5. Flüssige Zusammensetzung gemäß Patentanspruch 3 oder 4, wobei der besagte physiologisch aktive Wirkstoff in der besagten ständigen Phase enthalten ist.
- 30 6. Flüssige Zusammensetzung gemäß Patentanspruch 3 oder 4, wobei die Zusammensetzung in Form einer Dispersion ist, und wobei der besagte physiologisch aktive Wirkstoff in der besagten dispergierten Phase enthalten ist.
- 35 7. Flüssige Zusammensetzung gemäß einem der vorausgehenden Patentansprüche, wobei es sich bei dem besagten hydrophilen Polymer um Hydroxyalkylzellulose handelt.
- 40 8. Flüssige Zusammensetzung gemäß Patentanspruch 7, wobei es sich bei dem besagten hydrophilen Polymer um Hydroxypropylzellulose handelt.
- 45 9. Flüssige Zusammensetzung gemäß einem der vorausgehenden Patentansprüche, wobei es sich bei dem besagten hydrophoben Polymer um Octylacrylamid-Acrylat-Copolymer handelt.
- 50 10. Flüssige Zusammensetzung gemäß einem der Patentansprüche 1 bis 8, wobei es sich bei dem hydrophoben Polymer um einen Amino-Alkyl-Methacrylat-Copolymer handelt.
- 55 11. Flüssige Zusammensetzung gemäß einem der vorausgehenden Patentansprüche, wobei die Zuführungsgeschwindigkeit des besagten physiologisch wirksamen Wirkstoffes angepaßt werden kann, indem entweder das Verhältnis des hydrophilen Polymer zum wirksamen Wirkstoff, oder das Verhältnis des hydrophoben Polymer zum wirksamen Wirkstoff verändert wird.
12. Flüssige Zusammensetzung gemäß einem der Patentansprüche 1 bis 10, wobei die Zuführungsgeschwindigkeit des besagten physiologisch wirksamen Wirkstoffes angepaßt werden kann, indem das Verhältnis des hydrophilen Polymer zum hydrophoben Polymer verändert wird.

13. Flüssige Zusammensetzung gemäß einem der vorausgehenden Patentansprüche, die desweiteren einen Verdickungswirkstoff enthält, bei dem es sich nicht um Äthylzellulose handelt.
- 5 14. Flüssige Zusammensetzung gemäß Patentanspruch 13, wobei es sich bei dem besagten Verdickungswirkstoff um einen in sowohl Alkohol als auch Wasser löslichen Polymer handelt.
15. Flüssige Zusammensetzung gemäß einem der vorausgehenden Patentansprüche, wobei der Gesamtpolymergehalt der Zusammensetzung bis zu 50% Gesamtgewichtsanteil beträgt.

10

Revendications

1. Une composition liquide, en grande partie homogène, pour administration percutanée d'un [ou] plusieurs principes physiologiquement actifs dont la composition peut être appliquée à une surface de peau choisie de manière à former *in situ* un film de la composition adhérant à ladite surface de peau, la composition comprenant au moins un principe physiologiquement actif, un solvant volatil, un polymère hydrophile et un polymère hydrophobe :
- 20 le polymère hydrophile étant choisi entre l'hydroxypropylméthyl cellulose, l'hydroxypropyl cellulose, le polyvinylpyrrolidone, le carbopol, le polymère réticulé décadien de copolymère de vinylméthyléther et d'anhydride maléique et le guar hydroxypropylé et ses copolymères ; et le polymère hydrophobe étant choisi entre le copolymère acrylique d'octylacrylamide, le copolymère méthacrylique d'amino-alkyl, le copolymère ammonio méthacrylique, le copolymère de polyvinylpyrrolidone et d'acétate de vinyle, le PVAL, le copolymère d'ester butylique de polyvinylméthyléther et d'anhydride maléique, la laque en écaillles et les acrylates d'alkyle et leurs copolymères ; et de telle sorte qu'à l'utilisation les polymères hydrophile et hydrophobe présents dans la composition soient capables de moduler la vitesse d'administration dudit principe physiologiquement actif ; sous réserve que quand le polymère hydrophile est l'hydroxypropyl cellulose, le polymère hydrophobe ne soit pas un copolymère d'acrylate d'éthyle/méthacrylate de méthyle.
- 30 2. Une composition liquide définie à la revendication 1 et comprenant en outre un activateur de pénétration.
3. Une composition liquide définie à la revendication 1 ou 2 dans laquelle le polymère hydrophile soit capable de former une phase continue en application sur la peau d'un sujet et où le polymère hydrophobe soit dispersé ou soluble dans celle-ci.
- 35 4. Une composition liquide définie à la revendication 1 ou 2 dans laquelle le polymère hydrophobe soit capable de former une phase continue par application sur la peau d'un sujet et où le polymère hydrophile soit dispersé ou soluble dans celle-ci.
- 40 5. Une composition liquide définie aux revendications 3 ou 4 dans laquelle ledit principe physiologique actif soit contenu dans ladite phase continue.
6. Une composition liquide définie aux revendications 3 ou 4 telle que ladite composition soit sous la forme d'une dispersion et dans laquelle ledit principe physiologique actif soit contenu dans ladite phase dispersée.
- 45 7. Une composition liquide définie à l'une des revendications précédentes dans laquelle ledit polymère hydrophile soit une cellulose hydroxyalkylé.
8. Une composition liquide définie à la revendication 7 dans laquelle ledit polymère hydrophile est une cellulose hydroxypropylé.
- 50 9. Une composition liquide définie à l'une des revendications précédentes dans laquelle ledit polymère hydrophobe soit un copolymère acrylique d'octylacrylamide.
- 55 10. Une composition liquide définie à l'une des revendications 1 à 8 dans laquelle ledit polymère hydrophobe soit un copolymère méthacrylique d'amino-alkyl.
11. Une composition liquide définie à l'une des revendications précédentes dans laquelle la vitesse d'administration

dudit principe physiologique actif peut être ajustée en faisant varier soit le rapport du polymère hydrophile au principe actif soit le rapport du polymère hydrophobe au principe actif.

- 5 12. Une composition liquide définie à l'une des revendications 1 à 10 dans laquelle la vitesse d'administration dudit principe physiologique actif peut être ajustée en faisant varier le rapport du polymère hydrophile au polymère hydrophobe.
- 10 13. Une composition liquide définie à l'une des revendications précédentes ou suivantes comprenant un épaississant autre que l'éthyl cellulose.
- 15 14. Une composition liquide définie à la revendication 13 dans laquelle ledit épaississant est un polymère soluble à la fois dans l'alcool et dans l'eau.
15. Une composition liquide définie à l'une des revendications précédentes dans laquelle la teneur totale en polymères peut aller jusqu'à 50 % du poids.

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Fig 1.

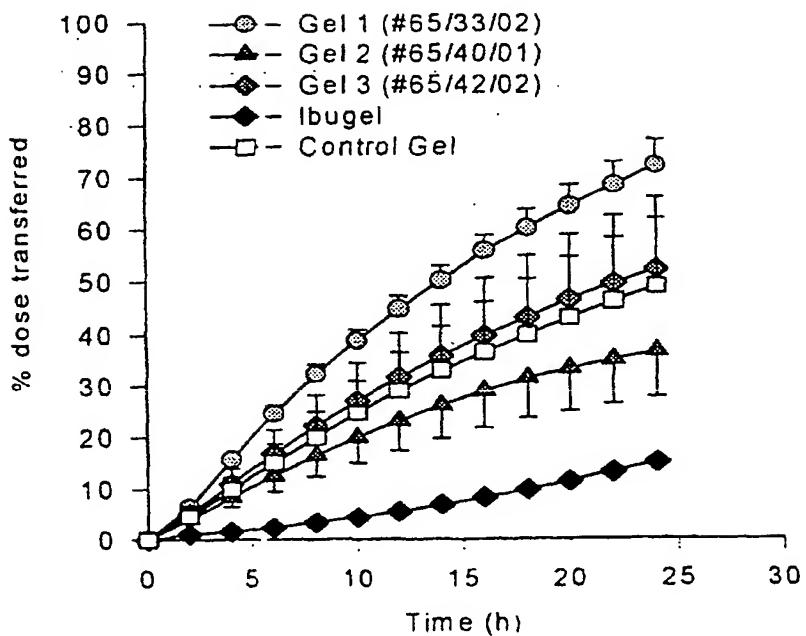
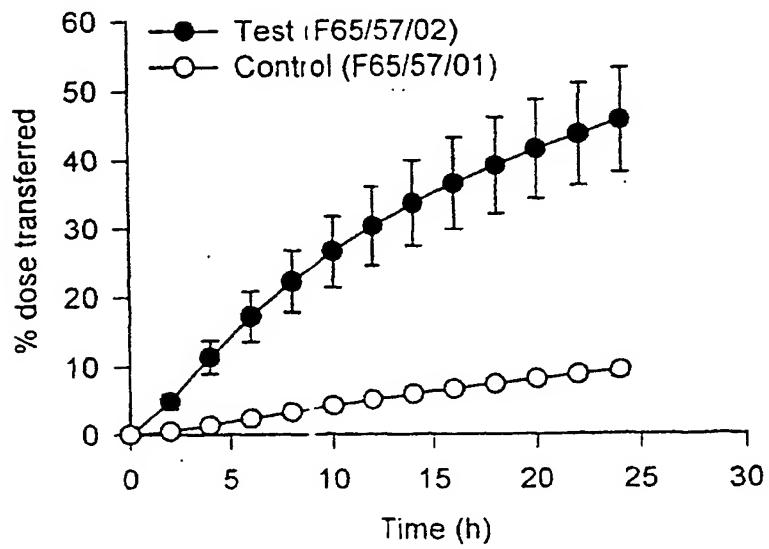


Fig 2.



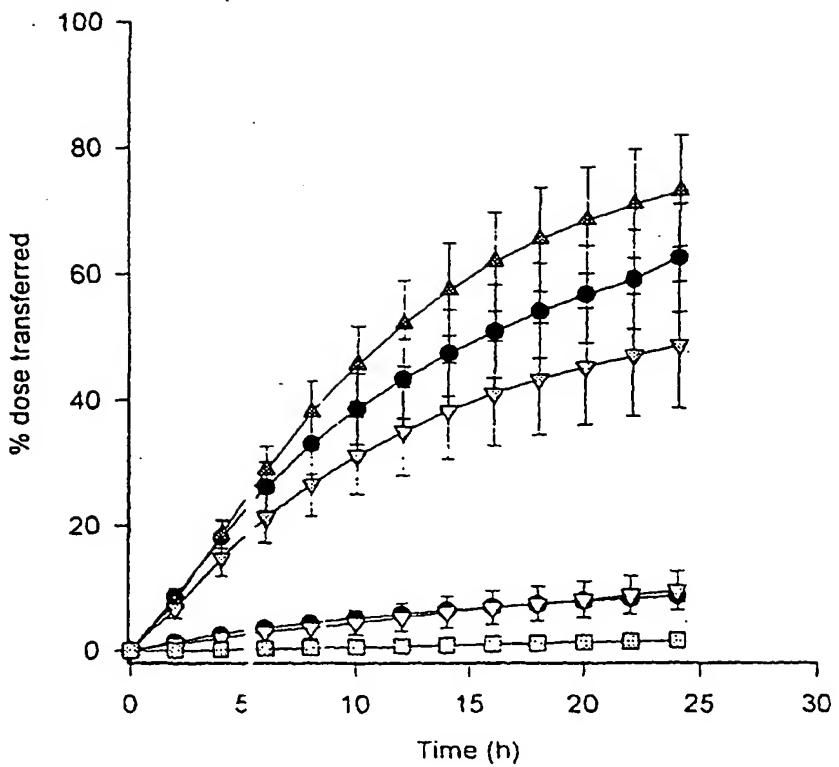


Fig 3.

- 1 (F71/05/01)
- ▲ 2 (F71/05/02)
- ▽ 3 (F71/05/03)
- 4 (F71/05/04)
- ▽ 5 (F71/05/05)
- 6 (Orudis™ Gel)

Fig 4. Liquipatch vs Commercial 1% clotrimazole cream.

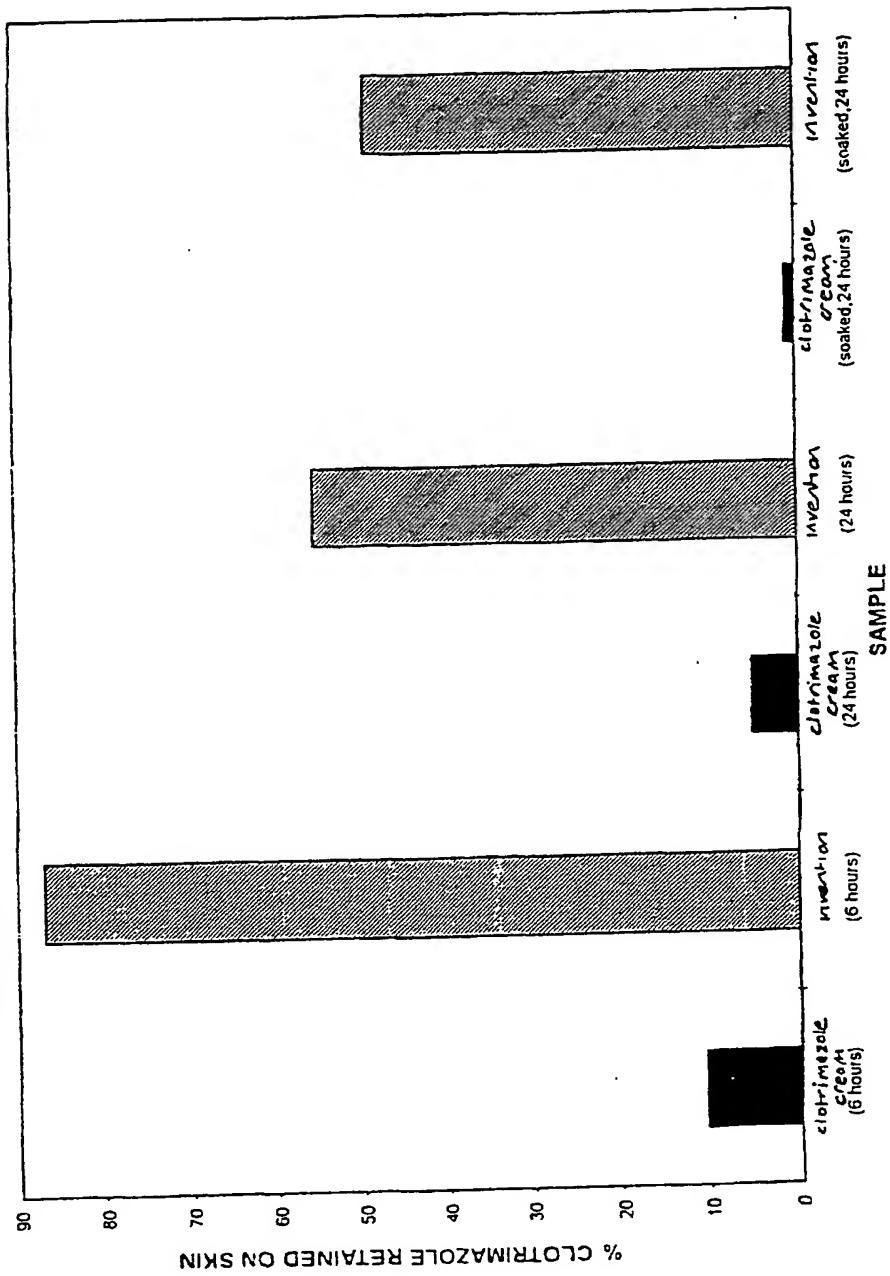


Fig 5.

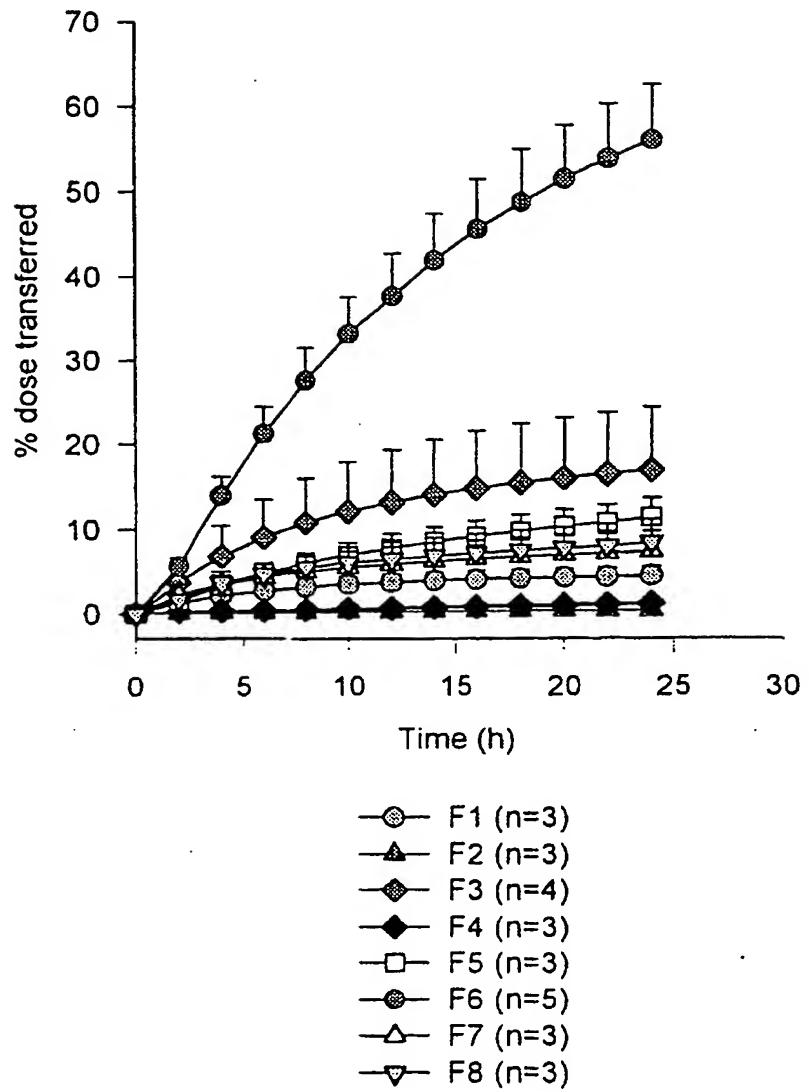


Fig 6.

